1. The Claims Are Clear and Definite

Claims 1-14 are objected to because of the preamble of Claims 1 and 9. While neither citing to the MPEP or to a statute, the Examiner is apparently making a rejection under 35 U.S.C. 112. Applicants submit that there is no ambiguity. Under 112 case law, claims are construed by one skilled in the art according to the specification. There is no basis offered by the Examiner to suggest that one skilled in the art would be unclear about the steps of the methods now claimed. There is no evidence whatsoever in the record that one skilled in the art would not understand how to carry out the methods now claimed. Thus, the rejection is unjustified. Nonetheless, to further the prosecution, and without waiving the right to prosecute the unamended claims in the future, the claims have been amended in the manner suggested by the Examiner.

2. Eibl (NEJM) Does Not Anticipate

Claims 1, 3, 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Eibl *et al.* (NEJM). The Examiner argues (see page 2) that Eible administers oral immunoglobulin "to inhibit the effects of anti-inflammatory mediators encompassing TNF in the infant's gut." It is respectfully submitted that the Examiner has misread the reference. Eibl notes that the antibody preparation is a commercially available IgA-IgG preparation known as IGABULIN (see page 7 of the article) which was simply made by fractionating human serum, *i.e.* without any use of antigen. Tables 1 and 2 show that the human serum fraction has some inherent reactivity with pathogens, including pathogens associated with necrotizing enterocolitis. There is no readily apparent evidence or data (and the Examiner points to none) supporting the notion that IGABULIN has antibodies to TNF. Indeed, the authors of the reference speculate that the mechanism of action is through pathogen binding:

> "Binding of an intact immunoglobulin to the antigen (e.g. a bacterial constituent) may reduce contact with the gut mucosa and facilitate the elimination of an excess of potentially pathogenic substances of alimentary, bacterial, or viral origin."

Thus, at best, the antibody preparation of the reference is directed to pathogen antigens. By contrast, the present claims say nothing about anti-pathogen antibodies. Rather, the present claims encompass an embodiment wherein a polyclonal antibody is used that was made by using TNF (or an epitope of TNF) as antigen, *i.e.* an antibody "*directed to* TNF". The Eibl reference describes no such thing and therefore cannot anticipate.

3. The Claims Are Not Obvious

Claims 1-14 are rejected under 35 U.S.C. 103(a) as allegedly obvious in light of Eible ('984 patent) or Lai ('532 patent) in view of Mugurum *et al.*, Eibl (NEJM) and further in view of Emery *et al.* (US Patent No. 5,420,253). Applicants respectfully submit that the Examiner has misread the references and not adhered to the proper standards for making a 103 rejection.

a. Eibl ('984) Teaches The Use Of Serum IgA

The Examiner, while admitting that "Eibl fails to specifically use anti-TNF antibodies in treating NEC," argues that "Eibl discloses methods of preparing and using anti TNF-α IgA antibodies to reduce the inflammatory response. . ." Applicants submit no such thing is taught in the '984 patent. The Abstract says nothing about TNF. Example VI (at column 11) simply measures the impact of IgA on TNF *production and/or release by monocytes!* Indeed, the authors implicitly rule out direct antibody inhibition of the cytokine:

> "The decrease . . . was due to a true down-modulation of the release of certain cytokines and not due to inhibition of cytokine detection."

Had the IgA directly bound the cytokines, there would have been inhibition of cytokine detection.[1] Instead, the antibody is reacting with the monocytes so as to cause "down-modulation" of cytokine production or release.

The Examiner is asked to take note of Example I and the description of the IgA actually used. The IgA was simply prepared by plasma fractionation - not by using TNF as an antigen. There is no evidence that such human plasma IgA reacts with TNF. In this sense, the '984 patent offers nothing more than the Eibl (NEJM) paper.

b. Lai Teaches Away

The Examiner, while admitting that "Lai . . . does not disclose administration of anti-TNF antibodies to human neonates," argues that the Lai patent teaches administering anti-TNF antibody, and points to the Abstract, text at column 2 (lines 35-55), text at column 7 (lines 1-5) and Example 4. Applicants note that the Abstract says nothing about TNF. The text at

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[1] Cytokine detection was carried out with commercially available ELISA kits. These kits contain the only anti-TNF antibody described in the patent - and the antibody is used to detect TNF in an ELISA format, not to reduce the inflammatory response.*in vivo*.

column 2 actually *teaches away* from the embodiment now claimed:

> ". . . TNF production peaks at about 1-2 hours. Therefore, in order to be effective, anti-TNF antibodies would have to be administered at an early stage after infection. Indeed in many clinical settings, patients are likely to already have been infected with facteria prior to being admitted. According *such therapeutic methods have met with only limited success.*"

(col.2, lines 35-41) (emphasis added). The Examiner is requested to note that this passage is in the BACKGROUND section of the Lai patent and is suggesting the inadequacy of the approach because of the alleged narrow window (early stage after infection) for treatment. The Lai patent goes on to contrast this approach and then concludes that one must deal with the "overproduction of nitric oxide."

This is a classic "teaching away" reference: "A reference may be said to teach away when a person of ordinary skill, upon [examining] (sic) the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Para-Ordnance Manufacturing v. SGS Importers International*, 37 USPQ2d 1237,1241 (Fed. Cir. 1995) (quoting *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994)). The Federal Circuit has said that discovering a method in the face of prior art which suggests that such a method would produce unacceptable results is the antithesis of obviousness. *See In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986). Thus, the Lai patent text, rather than supporting the Examiner's argument, undermines the Examiner's rejection.

Example IV (at column 11) teaches a "combinational therapy" involving anti-TNF antibodies. Moreover, the treatment is for LPS-induced shock - not NEC. Thus, Example IV cannot be said to add any support to the Examiner's argument.

c. Wolf/Eibl Teaches Only IGABULIN

The Wolf (Acta Pediatr. Suppl) adds nothing to the Examiner's argument. Like the Eibl (NEJM) paper, it teaches only the use of IGABULIN (see page 38, right column, bottom). This is not an antibody "directed to TNF." Moreover, Figure 1 is (like the Eibl patent) merely a demonstration of "down-modulation" - not inhibition of TNF by binding antibody to TNF itself.

d. The Proper Standards For A 103 Rejection Have Not Been Used

To establish *prima facie* obviousness, the Examiner must point to some motivation or suggestion within the references themselves, or within the knowledge generally available to one of ordinary skill in the art at the time of invention, to combine or modify the references.

See MPEP §2143.01; *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Merely because the references ***could be*** combined or modified does not render the resultant combination obvious unless the prior art suggested the combination. MPEP §2143.01; *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990).

Applicants submit that the references cannot be considered collectively until the Examiner points to some *evidence* to support combining those references. The purpose behind this requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent decision, articulates this position:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

See In re Rouffet et al., 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). It is readily apparent that the law of *In re Rouffet* requires the Examiner to present soundly reasoned arguments based upon the substance of the cited references.[2] Moreover, the law does not regard the Examiner as one skilled in the art. *See In re Rijckaert*, 28 USPQ2d 1955 at 1956 (Fed. Cir. 1993)("[T]he examiner's assumptions do not constitute the disclosure of the prior art."); *See id.* at 1957 ("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears."). Indeed, the Federal Circuit has made it clear that "[b]road, conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614 (Fed. Cir. 1999).

Applicants submit that the Examiner has not provided a sound explanation for combining these references as required by the law in *In re Rouffet*. What the Examiner has provided are unsupported and conclusory statements. Moreover, the Examiner proceeds from a flawed understanding of the references. In this regard, a review of Eibl II ('984) and Wolf/Eibl (Acta Pediat) reveals that these references are not teaching the use of an antibody "directed to TNF," but merely a human antibody fraction (from serum or plasma) with no

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[2] *Accord Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (stating that the examiner must present convincing line of reasoning supporting rejection).

apparent specific reactivity to TNF. Thus, these references - if they suggest anything - suggest that raising specific anti-TNF antibody is unncessary. The Lai reference suggests that anti-TNF treatment by itself is likely to be unsuccessful and focuses on overproduction of nitric oxide. Why would one skilled in the art combine such disparate art and techniques? The Examiner is reminded that there are many approaches to the treatment of disease. The Examiner has not provided an evidenciary basis for choosing the embodiment now claimed among the many approaches in the literature.

CONCLUSION

Applicants believe that the arguments set forth above traverse the Examiner's rejections and therefore request that these grounds for rejection be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (617)-252-3353.

Date 3/20/2003

By _____

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APPENDIX I
MARKED-UP VERSION OF AMENDED CLAIMS

Please amend the claims as shown below:

1. A method of treatment for necrotizing enterocolitis, comprising:

    a) providing:

        i) a human neonate, wherein said human neonate has symptoms of necrotizing enterocolitis;

        ii) a therapeutic formulation comprising polyclonal antibodies directed to TNF, and;

    b) administering said formulation to said human neonate.

9. A method of treatment for necrotizing enterocolitis, comprising:

    a) providing:

        i) a neonate at risk for necrotizing enterocolitis,

        ii) a therapeutic formulation comprising polyclonal antibody directed to TNF, and;

    b) administering said formulation to the lumen of the intestine of said neonate.